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(11)

EP 0 591 315 B1

(12)

EUROPEAN PATENT SPECIFICATION

(45) Date of publication and mention
of the grant of the patent:
07.05.1997 Bulletin 1997/19

(51) Int Cl. 6: G01N 33/52

(86) International application number:
PCT/GB92/01118

(21) Application number: 92913028.4

(87) International publication number:
WO 92/22815 (23.12.1992 Gazette 1992/32)

(22) Date of filing: 19.06.1992

(54) A porous membrane suitable for testing for the presence of a component in a biological fluid sample

Eine zur Bestimmung eines in einer biologischen Flüssigkeit enthaltenen Bestandteils geeignete, poröse Membran

Une membrane poreuse appropriée à la mise en évidence d'un composant dans un échantillon biologique liquide

(84) Designated Contracting States:
AT BE CH DE DK ES FR GB GR IT LI LU MC NL SE

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(43) Date of publication of application:
13.04.1994 Bulletin 1994/15

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(56) References cited:
EP-A- 0 256 806 EP-A- 0 265 253

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Description

The present invention relates to a support medium, notably to a support medium for a blood analysis reagent.

BACKGROUND TO THE INVENTION:

Typically, the analysis or testing of blood for the presence of glucose or other materials is carried out by applying a droplet of the blood to a test strip which carries a pad of a mixture of reagents which give a colour indication in response to one or more of the materials under test. The test strip typically carries the reagent(s) in a gelatin or other inert polymer or gel matrix pad at one end of a white plastic strip. However, this method suffers from the problems of contamination both of the sample by airborne and other materials and from the risk of cross-contamination of the samples on the test sticks where an operator is handling a number of tests simultaneously. It is also necessary to remove excess blood sample to enable the colour developing in the reagent pad to be observed, and this may lead to rupture or smearing of the reagent pad. There is also the problem of disposing of the bloodied test stick after the test has been completed.

It has been proposed, in for example US Patent 4,935,346, to apply the blood sample to one side of a translucent porous membrane carrying a reagent mixture within the pores so that the plasma of the blood flows into the pores and reacts with the reagent to develop a colour which is then observed from the other side of the membrane as it develops. Such a technique will be denoted hereinafter as a back reading technique.

However, we have found that if the pores are of a size which can be readily achieved with conventional manufacturing techniques, the surface tension effects at the entry to each pore passage are so great that the wall of a blood cell in contact with the face of the membrane is ruptured and the colour visible from the other face of the membrane is distorted by the presence of red cell wall fragments which have penetrated into the pores. It is therefore necessary to take extra colour readings to compensate for this distortion, which adds to the complexity of the process and the cost of devices for use therein.

It has been proposed to apply a surface coating to the membrane, including the internal walls of the pores thereof, so as to increase the cell protein binding properties of the membrane material. However, this treatment does not overcome the cell wall rupture problems described above and fragments of the cell wall still pass through the membrane to affect the colour observed.

We have now devised a means by which this problem can be reduced and by which a membrane suitable for use in the back reading technique can be produced. In our invention the pores which are initially present in the membrane are blocked or blinded so that there is no

free flow of fluid into the pores and the fluid component to be tested is separated by the membrane from cellular components of the material. The membrane can be mounted as an end wall of a chamber into which the blood is introduced for testing. The sample of blood is thus held enclosed within the chamber and the risk of external contamination and cross-contamination from other samples is reduced. Also, since the sample is retained within the chamber, the problems associated with disposal of the sample after testing are reduced.

SUMMARY OF THE INVENTION:

Accordingly, the present invention provides a porous membrane suitable for use as the support for testing for the presence of a component in a biological fluid sample applied thereto, characterised in that in at least part of their length the bores of the pores therein have been blinded with a material capable of forming a continuous solid, gel, or matrix form when introduced therein, whereby fragments of the wall of cells in a fluid sample applied to the membrane are substantially prevented from passing through the pores of the membrane, whereas the component to be tested is allowed to pass therethrough.

The invention provides a membrane suitable for use as the support for one or more test reagents for testing a material applied to the membrane, and particularly for use in a back reading technique in which blood plasma is separated from blood cells in a sample of blood applied to one surface of the membrane and the response of a reagent carried by the membrane is observed from another surface of the membrane, which membrane is characterised in that initially it is an open pored porous material and in that at least part of the length the pores therein are blinded so that cell wall fragments are substantially prevented from passage through the membrane. Preferably, at least 50%, eg more than 75%, of the length of the bores of the pores, notably substantially the whole length of the bores of the pores, are blinded and the blinding agent either substantially completely fills the cross-section of the bores or the bores are blocked to such an extent that the effective pore size of the membrane is reduced to a size below that at which rupture of the cell wall in the cellular component of the material applied to the membrane occurs to any significant extent.

Preferably, the membrane is a porous plastic sheet material, although other forms of membrane, for example a tube or other shaped member formed from or carrying the membrane can be used if desired. Thus, the membrane can be in the form of a conventional blood test stick. However, as stated above, the invention is of especial application in a back read test method, notably one in which the membrane forms one wall of a container for the fluid sample, so that the sample is held within the container and is isolated from the environment once it has been fed into the container.

The membrane forms a means for separating the non-cellular fluid from any cellular components of the fluid to be tested, and which allows the non-cellular fluid to pass into the material blinding the pores of the membrane with reduced cell wall rupture. For convenience, the invention will be described hereinafter in terms of this preferred application.

The membrane can be made from a wide range of materials having regard to the fluid to be applied to it, the size and nature of the cellular components therein and the test which is to be carried out on the non-cellular fluid component. Typically, the membrane will be a sheet of open pored porous plastic, notably one with an initial pore size which is smaller than the size of the cells which it is desired to separate out from the fluid. However, this need not be the case, since the blinding of the pores will reduce the effective pore size to substantially zero. It will be preferred for most uses that the membrane have an initial pore size in the range 0.1 to 10, notably less than 1, micrometres. The membrane may be made from a wide range of polymeric materials, for example cellulose, nitrocellulose and other cellulose derivatives such as cellulose esters; spun or woven polyamide fibres; polyvinylidene polymers; polycarbonate polymers; polysulfone polymers; polyalkylene polymers; acrylic or methacrylic acid polymers or co-polymers; polyamide polymers; polytetra-fluorethylene polymers and the like. The polymer will typically be in sheet form, but it may contain fibrous or other reinforcement if desired; or may be in the form of fine weave aperture woven fabrics. Such sheet materials will usually be flexible and will require mounting on a support member or the like for use. However, it is within the scope of the present invention to use a membrane in a rigid form, for example a sintered frit or ceramic having tortuous interconnecting interstices therethrough forming the pores which are to be blinded according to the invention. For convenience, the invention will be described hereinafter in terms of a sheet polymer as the membrane.

The pores can be formed within the membrane during its manufacture, as when a volatile material or a soluble salt or other material is incorporated into the polymers sheet, for example during calendering thereof, and this is subsequently evaporated or leached out of the polymer to leave a series of interconnecting passages or pores. Alternatively, the pores can be formed after manufacture of the sheet polymer, for example by needling or spark eroding the sheet polymer. Typically, the pores in the membrane will have a mean diameter of from 0.1 to 10 micrometres, preferably from 0.1 to 1 micrometre and the membrane will have an air permeability of from 1.5 to 4 litre, per minute per square centimetre at an applied pressure of 69 kPa (10 psig) across the plane of the membrane. Many forms of such membrane materials are available commercially and may be used in their commercially available form.

The membrane is preferably sufficiently thick that the colour of any blood cells retained on the face to

which the sample has been applied does not adversely affect the colour observed in the reagent with which the non-cellular components have interacted. Typically, the membrane will be from 50 to 500 micrometres thick so that excessive amounts of sample are not bound into the blinding material in the pore volume of the membrane.

The pores of the membrane are at least partially blinded by a material so that the initial pore size is reduced to a level at which either the surface tension effect at the entry to the pores is reduced to below that at which rupture of the cell wall is reduced and/or the pore is completely blocked by the blinding medium and thus does not cause rupture of the cells or does not allow the passage of significant amounts of cell wall fragments. Thus, the membrane can be padded in a fluid which carries solid particles suspended or dispersed therein or a colloidal solution of solid particles so that solid particles enter the pores and form a continuous mechanical blinding within the pores. In this case it may be desirable to apply a pre-coating to the pores to aid retention of the particles upon the walls of the pores. If desired, a thermoplastic or thermoset material can be used which is applied when molten, but which sets within the pores to form the blinding. The blinding agent may be one which sets in situ within the pores due to loss of water or due to a change in the rheological properties of the material, for example as when a fluid gels or a thixotropic material re-solidifies. Alternatively, the blinding material can be caused to set by a chemical change, as when a pre-polymer or monomer is caused to polymerise in situ. Where the blinding material does not set to a solid and/or might otherwise be susceptible to loss from the pores during storage and transit, it may be desirable to apply a sealing coating of a polymer or wax to the blinded membrane which is removed prior to use.

Typically, the material used to blind the bores of the pores is a material which readily wets the walls of the pores so as to reduce the formation of air pockets within the membrane; is a material which is inert to the reagents and the fluid to be tested; and preferably acts as a carrier for the reagents to be used in the test so as to form a translucent matrix within the bore so that the colour developed within the bore of the pore can be observed.

The blinding agent will often act as the medium through which the products of the interaction of the material under assessment with one or more of the reagents in the matrix diffuse to interact with other components, for example a chromogen. It is therefore preferred that the blinding of the pores form a continuous solid or matrix body within the pore, rather than a plug of solid particles with fine interconnecting interstices throughout the plug, so that this diffusion may take place. This is particularly important where interaction between the fluid being assessed and an enzyme reagent takes place to release a product, for example hydrogen peroxide, which then reacts with another com-

ponent, for example the chromogen o-tolidine, to give a colour which is observed from the exposed outer face of the membrane. In a particularly preferred embodiment, an aqueous solution or colloidal suspension of gelatin is used to form a gel plug within all or part of the length of the pore bores. The gelatin for present use preferably has a low or medium molecular weight, for example with an average molecular weight within the range 2,000 to 50,000. Such forms of gelatin are commercially available and may be used in their commercially available forms. If desired, the commercial material can be subjected to a pretreatment, for example acid washing or other conventional treatment, to render it suitable for use in blood analysis or testing.

The blinding of the pores can be carried out so that the whole length of each bore is blinded. However, this is often not necessary and blinding of only part of the length of the pore bores may give satisfactory results. The amount of blinding agent applied to a membrane will depend upon the pore diameter, the thickness of the membrane, the material to be tested and the nature of the test to be carried out. The optimum amount can readily be established by simple trial and error tests for any given case. However, where a gelatin blinding agent is used, we have found that the application of from 1 to 10, eg. 2 to 6, milligrams of gelatin per square metre of a 0.1 to 0.5 mm thick membrane will usually be required. The blinding is preferably carried out so as to blind the whole plan area of the membrane. However, it may be desired to provide the blinding to only a selected area of the membrane to which the blood or other material to be tested is applied. Alternatively, the membrane can be cut into discs or strips to provide the desired area of treated membrane.

The blinding material can be applied to the membrane by any suitable method. For example, a solution or suspension of the material can be applied by spraying dipping, roller coating or padding to the membrane so as to load the membrane with the desired amount of blinding material. In the case of gelatin, the concentration of the gelatin in the total blinding mixture applied to the membrane can vary from about 400 parts by weight per 600 parts by volume of water or other carrier fluid for a gelatin having an average molecular weight of 2-3,000, to 100 parts by weight per 600 parts by volume of the carrier fluid for a gelatin having an average molecular weight in the range 25,000 to 40,000. The material can be assisted into the bores of the pores by applying suction to one face of the membrane to draw material into the pores and/or by applying a hydrostatic head to the membrane to force the blinding material into the pores.

As indicated above, the membranes of the invention find especial use to support reagents for some test to be carried out on a fluid applied to the membrane. For example, the membrane can support a surface coating of the reagents on that face opposed to the one to which the sample is applied so that the non-cellular fluid from

the sample penetrates through the blinded pores and contacts the reagent layer. However, it is preferred that the reagents be incorporated in the blinding within the pores, for example by incorporating the appropriate reagents in an aqueous gel applied to the membrane, so that the non-cellular fluid interacts with the reagents in the pores of the membrane to provide a colouration to the blinding which can be observed from the other face of the membrane.

The membranes of the invention can be used in a wide range of applications where it is desired to separate the non-cellular fluid from the cellular components of a fluid for testing. Thus, the membranes can be used in the assessment of plant cellular materials and the like. However, the invention is of especial application in testing blood or other bodily fluids, cellular materials and the like. However, the invention is of especial application in testing blood or other bodily fluids, notably for the glucose, urea or cholesterol content thereof.

DESCRIPTION OF THE DRAWINGS:

The invention will now be described by way of illustration with respect to a preferred form thereof as shown in the accompanying drawings in which Figure 1 is a diagrammatic sectional view through a membrane of the invention; and Figure 2 shows the membrane is use in a back reading technique testing device.

DESCRIPTION OF THE PREFERRED EMBODIMENT

A first solution was made by stirring together at room temperature 300 ml of de-ionised water, 200 ml of 0.5 Molar sodium phosphate buffer to give a pH of 7, 100 ml of a 20% w/v solution of the surfactant Gantrez and 300 g of dry powdered gelatin having a molecular weight in the range 2,500 to 4,000.

A second solution was prepared by stirring together at 60° C for one hour 300 ml of de-ionised water, 300 ml of methoxyethanol and 15 g of o-tolidine hydrochloride or dianisidine hydrochloride.

The second solution was mixed dropwise with stirring into the first solution and the mixture stood for 1 hour at 60° C.

A third solution was made up by mixing 500,000 IU of glucose oxidase and 300,000 IU of peroxidase in 0.1 Molar solution of the sodium phosphate buffer. This solution was mixed with stirring into the other mixed solutions and filtered through a 0.1 micrometre aperture filter.

The resultant solution was impregnated into a polysulfone resin sheet 1 (0.2 to 0.4 mm thick and having a pore diameter of 0.2 micrometres and an air permeability of 3 litres per minute per square centimetre at an applied pressure of 69 kPa (10 psig)) to provide 5 IU of glucose oxidase, 3 IU of peroxidase, 0.2 milligrams of o-tolidine and 4 milligrams of gelatin per square centimetre of the membrane 1. The impregnation was car-

ried out by padding the membrane sheet through the aqueous solution. Since the polysulfone resin is hydrophobic, the gelatin solution wets the internal surfaces of the pores and the capillary action of the pores readily ensures that the gelatin solution enters the pores.

The padding is carried out first with the membrane one way up until the solution wets the upper surface of the membrane, then the other way up so that the pores 2 are substantially filled with the gelatin solution. The loaded membrane is allowed to dry so that a solid plug 3 of the gelatin gel is formed within the pores.

The membrane is cut into discs 10 which are used to form the end wall of a test chamber 11 having an open top or bore 12 into which a drop of blood 13 can be fed. The blood enters the chamber 11 so that it is held wholly within the test device 14. The blood 13 wets the inner face of the membrane and the non-cellular plasma penetrates the pores 2 by absorption or solution in the gelatin plug 3. The blood cells are prevented from entering the pores by the gelatin plug and little or no rupture of the blood cells occurs.

As the plasma diffuses through the gelatin matrix blinding the pores, it interacts with the reagents and gives a colour change which can be observed from the outer face of the device, as shown by the arrow. In this way the blood sample is not exposed to contamination and the test device can be disposed of without the risk of infection from the blood contained therein. The membrane of the invention reduces the rupture of the blood cells and thus reduces the colouration observation errors due to blood cell fragments.

From a preferred aspect, the present invention thus provides a method for testing blood, which method comprises applying a sample of the blood to a first surface of an initially porous membrane, which membrane carries a gelatin based matrix containing at least one reagent to respond to a component in the blood therein, the said matrix substantially completely blinding the pores in the membrane in the area to which the said sample is applied, whereby red blood cells in the said sample are retained substantially unruptured at said first surface and the plasma of the said sample passes into the said matrix to interact with said reagent to produce a colour, and observing the colour from a second surface of said membrane.

The invention also provides a method for producing a membrane of the invention, which method comprises applying a fluid composition containing a blinding material to an initially porous membrane whereby the fluid penetrates the bores of the pores of the membrane; and allowing the composition to solidify so as to form a solid within the said pores which substantially completely occupies at least part of the length of the bores of the pores.

Claims

1. A porous membrane suitable for use as the support for testing for the presence of a component in a biological fluid sample applied thereto, characterised in that in at least part of their length the bores of the pores therein have been blinded with a material capable of forming a continuous solid, gel, or matrix form when introduced therein, whereby fragments of the wall of cells in a fluid sample applied to the membrane are substantially prevented from passing through the pores of the membrane, whereas the component to be tested is allowed to pass there-through.
2. A membrane as claimed in claim 1, wherein substantially the whole length of the bores of the pores of the membrane are blinded, and the blinding material substantially completely fills the cross-section of the bores.
3. A membrane as claimed in either of claims 1 or 2, wherein the bores of the pores of the membrane are blinded by a material containing at least one reagent which reacts with a component in the fluid sample to be tested.
4. A membrane as claimed in any one of the preceding claims wherein the blinding material is a gelatin.
5. A membrane as claimed in any one of the preceding claims, wherein the membrane is a polysulphone resin.
6. A fluid testing device incorporating a membrane as claimed in claim 1.
7. A device as claimed in claim 6, wherein the device comprises a sample retaining chamber having one wall thereof formed at least in part by the membrane and adapted to be contacted by a sample introduced into said chamber.
8. A method for testing a fluid sample which comprises applying it to a first surface of a membrane as claimed in claim 1 carrying a reagent which interacts with a component of the fluid sample upon a second face of the membrane and/or in the pores of the membrane; and observing the interaction of a component of that fluid sample with the reagent through said second surface of said membrane.
9. A method as claimed in claim 8, wherein the fluid sample being tested contains cellular material and the cellular material is retained at said first surface by said blinding of the membrane.
10. A method for testing blood, which method compris-

es applying a sample of the blood to a first surface of a porous membrane which carries a gelatin based matrix containing at least one reagent which reacts with a component in the blood, the said matrix substantially completely blinding the pores in the membrane, whereby red blood cells in the said sample are retained substantially unruptured at said first surface and the plasma of the said sample passes into the said matrix to react with said reagent to produce a colour, and observing the colour from a second surface of said membrane.

11. A method for producing a membrane as claimed in claim 1, which comprises applying a fluid composition containing a blinding material to an initially porous membrane whereby the fluid penetrates the bores of the pores of the membrane; and allowing the composition to solidify so as to form a continuous solid, gel, or matrix within the said pores which substantially completely occupies at least part of the length of the bores of the pores.

Patentansprüche

1. Poröse Membran, die zur Verwendung als Träger für die Bestimmung des Vorhandenseins eines Bestandteils in einem biologischen Fluid geeignet ist, dadurch gekennzeichnet, daß die Öffnungen der Poren mindestens über einen Teil ihrer Länge mit einem Material aufgefüllt sind, das darin eingefüllt einen kontinuierlichen Festkörper, ein Gel oder eine Matrix-Form bilden kann, wobei Fragmente von Zellwänden in einer auf die Membran aufgetragenen Fluidprobe im wesentlichen am Durchgang durch die Poren der Membran gehindert werden, wohingegen der zu bestimmende Bestandteil durch sie hindurchgehen kann.
2. Membran nach Anspruch 1, wobei im wesentlichen die gesamte Länge der Öffnungen der Poren der Membran aufgefüllt ist und das Auffüllmaterial den Querschnitt der Öffnungen im wesentlichen vollständig ausfüllt.
3. Membran nach Anspruch 1 oder 2, wobei die Öffnungen der Poren der Membran mit einem Material aufgefüllt sind, das mindestens ein Reagens aufweist, das mit einem Bestandteil in der zu überprüfenden Fluidprobe reagiert.
4. Membran nach einem der vorangehenden Ansprüche, wobei daß das Auffüllmaterial eine Gelatine ist.
5. Membran nach einem der vorangehenden Ansprüche, wobei die Membran ein Polysulfon-Harz ist.
6. Vorrichtung zur Fluidüberprüfung mit einer Mem-

bran nach Anspruch 1.

7. Vorrichtung nach Anspruch 6, mit einer Probenrückhalte-Kammer, deren eine Wand mindestens teilweise von der Membran gebildet ist, und die dafür ausgebildet ist, mit einer in die Kammer eingebrachten Probe in Kontakt zu treten.
8. Verfahren zur Überprüfung einer Fluidprobe, bei dem die Fluidprobe auf eine erste Oberfläche einer Membran gemäß Anspruch 1 aufgebracht wird, wobei die Membran ein Reagens beinhaltet, das auf einer zweiten Oberfläche und/oder in den Poren der Membran mit einem Bestandteil der Fluidprobe wechselwirkt, und die Wechselwirkung eines Bestandteils der Fluidprobe mit dem Reagens durch die zweite Oberfläche der Membran beobachtet wird.
9. Verfahren nach Anspruch 8, wobei die zu testende Fluidprobe Zellmaterial enthält und das Zellmaterial durch die Auffüllung der Membran an der ersten Oberfläche zurückgehalten wird.

10. Verfahren zur Überprüfung von Blut, wobei in dem Verfahren eine Probe des Blutes auf eine erste Oberfläche einer porösen Membran, die eine gelatinebasierte Matrix mit mindestens einen mit einem Bestandteil des Blutes reagierenden Reagens aufweist, aufgebracht wird, die Matrix in wesentlichen die Poren der Membran vollständig auffüllt, wobei rote Blutkörperchen in der Probe im wesentlichen unverletzt an der ersten Oberfläche zurückgehalten werden, und das Plasma der Probe in die Matrix eintritt, um mit dem Reagens zu reagieren und eine Farbe hervorzurufen, und die Farbe von einer zweiten Oberfläche der Membran beobachtet wird.
11. Verfahren zur Herstellung der Membran nach Anspruch 1, wobei eine flüssige Zusammensetzung, die ein Auffüllmittel enthält, auf eine anfangs poröse Membran appliziert wird, wobei das Fluid in die Öffnungen der Poren der Membran eindringt, und die Zusammensetzung zur Bildung eines kontinuierlichen Festkörpers, eines Gels oder einer Matrix innerhalb der Poren erstarren kann, so daß mindestens ein Teil der Länge der Öffnungen der Poren im wesentlichen vollständig ausgefüllt ist.

Revendications

1. Membrane poreuse convenant à l'utilisation comme support pour tester la présence d'un composant dans un échantillon de fluide biologique appliqué sur celle-ci, caractérisée en ce qu'au moins une partie de la longueur des perforations des pores a été rendue borgne à l'aide d'un matériau pouvant for-

- mer un gel solide continu ou une forme de matrice lors de son introduction, de sorte que des fragments de la paroi de cellule dans un échantillon de fluide appliqué sur la membrane sont sensiblement empêchés de traverser les pores de la membrane tant que le composant à tester peut les traverser. 5
2. Membrane selon la revendication 1, dans laquelle sensiblement toute la longueur des perforations des pores de la membrane a été rendue borgne et le matériau de réalisation des trous borgnes remplissant sensiblement de façon complète la section transversale des perforations. 10
3. Membrane selon l'une quelconque des revendications 1 ou 2, dans laquelle les perforations des pores de la membrane sont rendues borgnes par un matériau contenant au moins un agent réactif qui réagit avec un composant dans l'échantillon de fluide à tester. 15 20
4. Membrane selon l'une quelconque des revendications précédentes, dans laquelle le matériau de réalisation des trous borgnes est une gélatine. 25
5. Membrane selon l'une quelconque des revendications précédentes, dans laquelle la membrane est une résine de polysulfone.
6. Dispositif de test de fluide incorporant une membrane selon la revendication 1. 30
7. Dispositif selon la revendication 6, dans lequel le dispositif comprend une chambre de retenue d'échantillon dont une de ses parois est formée au moins en partie par la membrane et peut être mise en contact par un échantillon introduit dans la chambre. 35
8. Procédé pour tester un échantillon de fluide qui comprend l'application de celui-ci sur une première surface de la membrane selon la revendication 1, comportant un réactif qui interagit avec un composant de l'échantillon de fluide sur une seconde face de la membrane et/ou dans les pores de la membrane ; et mise en observation de l'interaction d'un composant de cet échantillon de fluide avec le réactif par la seconde surface de cette membrane. 40 45
9. Procédé selon la revendication 8, dans lequel l'échantillon de fluide en cours de test contient un matériau cellulaire et le matériau cellulaire est retenu sur la première surface en rendant les perforations de la membrane borgnes. 50 55
10. Procédé pour tester le sang, lequel procédé comprend l'application d'un échantillon du sang sur une première surface d'une membrane poreuse qui supporte une matrice à base de gélatine contenant au moins un agent réactif qui réagit avec un composant dans le sang, la matrice rendant les pores borgnes sensiblement complètement dans la membrane, de sorte que les hématies dans l'échantillon sont retenues sensiblement sans rupture au niveau de la première surface et le plasma de l'échantillon passe dans la matrice pour réagir avec l'agent réactif et produire une couleur ; et l'observation de la couleur à partir d'une seconde surface de la membrane.
11. Procédé pour la production d'une membrane selon la revendication 1, qui comprend l'application d'une composition de fluide contenant un matériau pour rendre les perforations borgnes sur une membrane initialement poreuse de sorte que le fluide pénètre dans les perforations des pores de la membrane ; et en laissant la composition se solidifier de façon à former un gel solide continu ou une matrice à l'intérieur des pores occupant de façon sensiblement complète au moins une partie de la longueur des perforations des pores.

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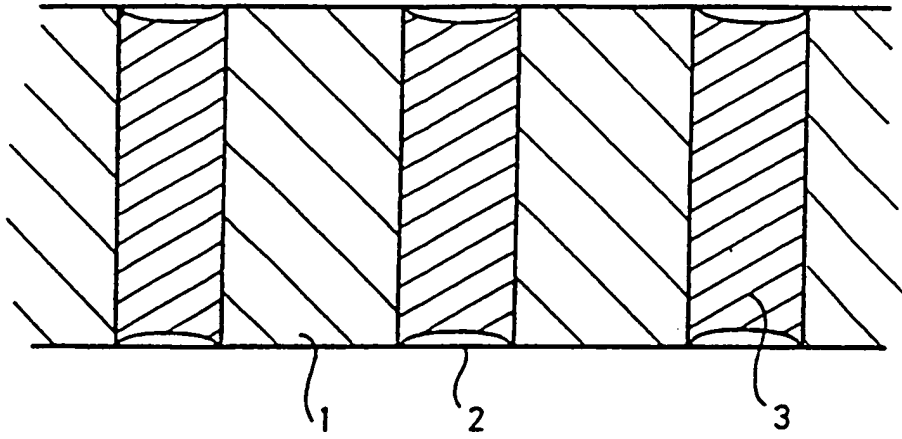


Fig. 1

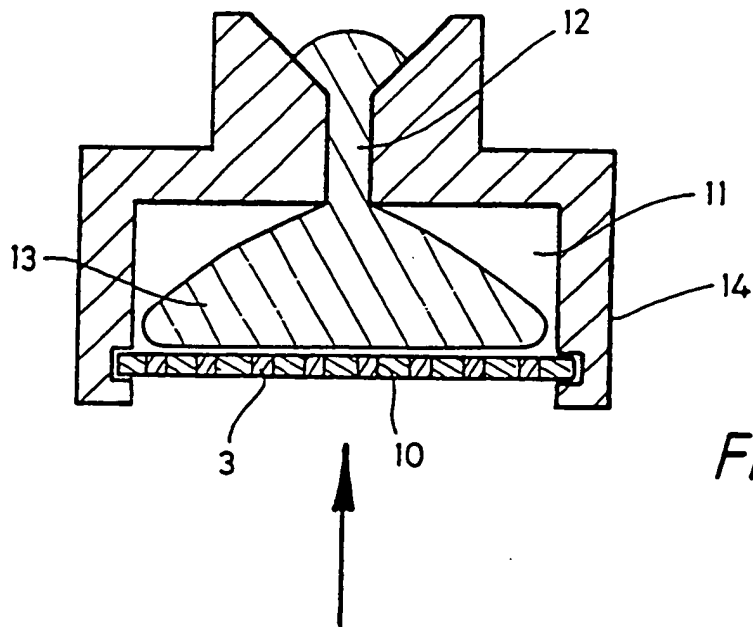


Fig. 2

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